18

CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

Additional copies are available from:
Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
5600 Fishers Lane
Rockville, MD 20857

(Tel) 301-827-4573
(Internet) http://www.fda.gov/cder/guidance/index.htm

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

Center for Drugs and Biologics
Food and Drug Administration
Department of Health and Human Services

GUIDELINE FOR SUBMITTING DOCUMENTATION

FOR THE STABILITY OF HUMAN DRUGS AND BIOLOGICS

February 1987

The degradation curve is estimated most precisely (in terms of the width of the confidence intervals about the estimated curve, as illustrated in Figure 1) around the average of the sampling times included in the study. Therefore, testing an increased number of replicates at the later sampling times, particularly the latest sampling time, is encouraged, because this will increase the average sampling time toward the desired expiration dating period.

2. Data Analysis and Interpretation; Long-Term Studies

The methods described in this section are used to establish, with a high degree of confidence, an expiration dating period during which the average drug product characteristic (e.g., strength) of the batch will remain within specifications. This expiration dating period should be applicable to all future batches produced by the manufacturing process for the drug product. It is not sufficient that a proposed expiration dating period ensure that the process average is within specifications, if a substantial number of individual batch averages are out of specifications at the end of the proposed expiration dating period.

If an applicant chose an expiration dating period to ensure that the characteristics of a large proportion of the individual dosage units are within specifications, different statistical methods than those proposed below would be needed. For example, see Easterling (Ref. 12). Also, it would be necessary to test individual units rather than composites. However, as noted before, the following represents an acceptable approach.

a. Determining the allowable expiration dating period for an individual batch: The time during which a batch may be expected to remain within specifications depends not only on the degradation rate, but also on the initial average value for the batch. Thus any information on the initial value for the batch, such as the results of release testing on that batch, is relevant to the determination of the allowable expiration dating period and should be included in the stability study report. Also, percent of label claim, not percent of initial average value, is the variable of interest.

When establishing the expiration dating period for an individual batch, support is obtained from the observed pattern of degradation for the quantitative drug product characteristic under study (e.g., strength) and to the

precision by which it is estimated. An acceptable approach for drug characteristics that are expected to decrease with time is to determine the time at which the 95% one-sided lower confidence limit (sometimes called the 95% lower confidence bound) for the mean degradation curve intersects the acceptable lower specification limit.

Carstensen and Nelson (Ref. 13) proposed an approach equally acceptable to this, and the 95% lower confidence limit for the mean is described in their paper and is illustrated in their Figure 1, labeled Roman Numeral I. Note, however, that Carstensen and Nelson proposed that the expiration dating period be determined on the basis of a different curve (the so-called "prediction limit," labeled Roman Numeral II in their Figure 1) than is presented here. In the example shown in our Figure 1 (where the lower specification limit is assumed to be 90% of label claim) an expiration dating period of four years would be granted. For drug product characteristics expected to increase with time (e.g., there may be an upper limit on the amount of certain degradation products), the 95% one-sided upper confidence limit for the mean would be used.

For drug product characteristics with both an upper and a lower specification limit, there may be special cases where it would be appropriate to use the two-sided 95% confidence limits. As an example, suppose the drug characteristic of interest was concentration of unchanged active ingredient for a solution. Chemical degradation of the active ingredient would decrease the concentration. On the other hand, evaporation of the solvent (possibly resulting from the characteristics of the closure) would increase the concentration. Since both possibilities must be allowed for, two-sided confidence limits would be appropriate. (If both mechanisms were acting, however, the concentration might decrease initially and then increase. In this case, the degradation pattern would not be linear and more complicated statistical methods would be needed.)

If the approach of this section is used, we may be 95% confident that the average drug product characteristic (e.g., strength) of the dosage units in the batch is within specifications up to the end of the expiration dating period. It is not acceptable to determine the allowable expiration dating period by determining where the fitted least-squares line intersects the appropriate specification limit. This approach is as likely to

overestimate the expiration dating period as to underestimate it (i.e., we may only be 50% confident that the batch average is within specifications at expiration if the fitted least-squares line is used).

The statistical assumptions underlying the procedures described above (e.g., the assumption that the variability of the individual units from the batch average remains constant over the several sampling times) are well known and have been discussed in numerous statistical texts. The above procedures will remain valid even when these assumptions are mildly violated. If there is evidence of severe violation of the assumptions in the data, an alternate approach may be necessary to accomplish the objective of determining an allowable expiration dating period with a high degree of confidence that the period does not overestimate the true time during which the drug product remains within specifications.

There may be cases where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested expiration dating period will be confirmed. Under these circumstances it would not be necessary to go through

the formal calculations involved in the above analysis. However, this case is the exception rather than the rule, and the final judgment on whether the calculations are necessary lies with the reviewers in the CDB. Consequently, failure to include the results of the analyses described above could result in a delay of the stability review, if the reviewers feel that the calculations are needed. Therefore, it is recommended that the analyses be carried out routinely.

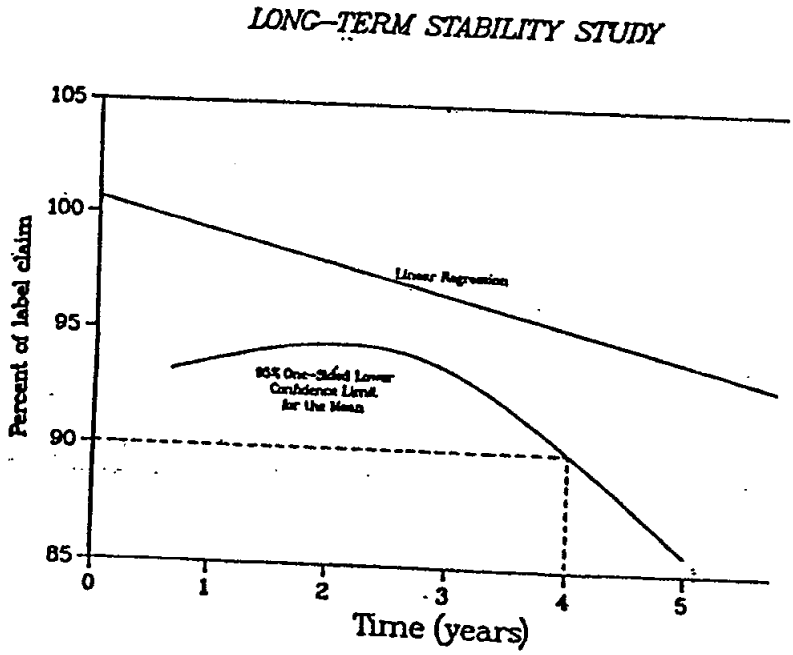

Figure 1